TRANSITIONING FROM LAB TO MARKET: AN ANALYSIS OF CRISPR'S IMPACT IN REVOLUTIONIZING THE COMMERCIALIZATION OF GENOME-EDITING TECHNOLOGY

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ABSTRACT

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Since the 1970s, when the era of genome-editing technology began with the introduction of recombinant DNA, a lot of research conducted in labs transitions into practical applications that consumers see on the market. The recent discovery of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), a new genome-editing tool, is disrupting genome-editing technology's path to commercialization. This thesis aims to address the lessons learned from the case study of the Flavr Savr tomato, the first commercialized food product in the U.S., and how those lessons provide insight to the implications of commercially using CRISPR. Then, more broadly, this examination analyzes how awareness of CRISPR's complexities and the intersection between science and business suggests that commercialization of genome-editing technology needs to be more efficient in the evolving landscape of genome editing.

The first task is to understand the role of genome-editing technology in establishing the context in which CRISPR is introduced. The second task involves discussing the complexities of using CRISPR, focusing on the legal and ethical implications. The third task is to compare the case study of the CRISPR application in sickle-cell anemia to that of antisense technology, an earlier discovered genome-editing technology, application in the Flavr Savr tomato. Lastly, this thesis will evaluate the impact of CRISPR's development on genome-editing technology's commercialization path and put forth recommendations on how to bridge some of the disconnect between science and business in order to make the commercialization process more efficient.

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Introduction

A seemingly small change can lead to significantly large effects. Take for example how a single genetic mutation in a letter of DNA can lead to the production of "sickle"-shaped red blood cells and result in fatal consequences. Or consider how the implementation of a new tool can lead to treatments for genetic diseases and a reduction of millions of dollars in research and development costs. These situations are applicable to and all too familiar in the realm of molecular biology, and specifically genome editing. They also precisely describe the phenomenon of *The Butterfly Effect*, which captures how the sensitivities of small actions are magnified to large-scale, potentially serious implications. In genome editing, the introduction of a new paradigm can produce unexpected outcomes due to insufficient regulation of scientific freedom within the lines of business and unclear understanding of the general mechanisms and potential applications of genome-editing technologies. Those outcomes can have a significant effect when they translate into the development of practical applications, such as genetically-engineered food or drugs and vaccines, that the general public will be exposed to on a regular basis, whether we are aware of these changes or not.

Genome editing, a type of genetic engineering, involves inserting, deleting, or replacing DNA at a particular location in an organism's or cell's genome. It is often performed in the lab with the use of engineered nucleases, also referred to as *molecular*

scissors.[1] Genome editing has great promise for application in a variety of potential commercial applications, from developing anticancer immunotherapies to producing biofuels. The versatility of genome editing has made it a "powerful tool in basic biological research."[2] The genetic engineering age began in the 1970s when Herbert Boyer of Stanford University and Stanley Cohen of the University of California, San Francisco (UCSF) developed the technique to recombine the genes in bacterial plasmids – this technique is known as recombinant DNA technology.[3,4]

In the late 1970s, Genentech, Boyer's biotechnology company, applied the recombinant DNA technology to modify *E. coli* to contain a synthetic human gene. In the lab, the genetically engineered *E. coli* was then used to produce insulin for diabetics. This early move of transitioning genome-editing technology from research labs into the commercial sector demonstrated the potential that the benefits of science could extend beyond research in the lab to the reaches of our communities. Take for instance the discovery of DNA's structure – the research on DNA's structure has helped to create tests that detect genetic diseases and has even made DNA fingerprinting an instrumental technique in forensic testing. Technology commercialization is, in principle,

[1] Gene Editing
[2] Egelie, K. J., Graff, G. D., Strand, S. P., & Johansen, B. (2016, October). The emerging patent landscape of CRISPR-Cas gene editing technology.
[3] Russo, E. (2003, January). Recombinant DNA: The First Report | The Scientist Magazine(R).
[4] Knox, M. (2014, December 1). Is the Gene-Editing Revolution Finally Here?

about identifying a market for a specific technology.[5] In the case of commercializing genome-editing technology, the process relies on the ability to efficiently move a product, a genome-editing technology, as a concept from the lab to a practical application on the market.

Making observations and building upon them to conduct research and ultimately make predictions and discoveries about our world is the core of science. The vehicles that help drive those observations and predictions forward stem from the use of scientific tools, and in the world of genome editing, we have various technologies to select from, including zinc-finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and antisense technology.

In the 1990s, antisense technology was used to create the Flavr Savr tomato, the first commercialized food product in the U.S. The Flavr Savr tomato case used antisense technology, a genome-editing technology, to grow the fresh tomato market – I will further explore the case in this thesis. Among the current genome-editing technologies, Clustered Regularly Interspaced Short Palindromic Repeats, also known as CRISPR, is the most recently introduced "molecular scissors". It has held the attraction of the scientific world and is attracting the investment of the business world.

[5] Fletcher, A. C., & Bourne, P. E. (2012, September 27). Ten Simple Rules to Commercialize Scientific Research.

In this thesis, I address the question: how do the lessons from the use of antisense technology in the Flavr Savr tomato case provide insight about the implications of commercializing CRISPR today? To address this question, I will first introduce what the technology is, providing a general explanation of its mechanism and characteristics. Then I explore the complexities of CRISPR, targeting the legal and ethical implications, and incorporating personal interview responses from CRISPR researchers to better inform my main question. Limitations in the design and operation of past technologies have hindered those technologies from conquering the challenge of precisely editing specific DNA sequences. I will discuss why CRISPR is a tool that holds the potential promise of addressing that challenge.

I then undertake a case study of CRISPR in sickle-cell anemia that has the potential to undergo commercialization. This case is a prime candidate to explore three implications of commercializing CRISPR I will address in this thesis: ethical considerations, legal considerations, and the growing disconnect between science and business. I will compare this CRISPR study to that of an antisense technology study based on the Flavr Savr tomato by critically examining the three factors mentioned above.

I conclude by offering recommendations on how we can more efficiently bridge the disconnect between science and business in order to establish an ethically mindful context in which everyone, including the general public, understands the significance

and implications of CRISPR as well as that of genome-editing technology. The realms of science and business have clashing values and practices, and these differences are most apparent when the two realms intersect and seek to collaborate. As science and business interact to enable CRISPR to solve real world problems, we need to determine how to better manage the business of science.

In this thesis, I discuss only one of CRISPR's paths to commercialization, though there may be many different paths. Many genome-editing technologies started from industry, but academic research institutions pioneered CRISPR.[6] Academic research institutions have different resources and access to business expertise to commercialize genome-editing technologies compared to those found in industry. In academia, research can be valuable, yet after publication of research results, that value may only be of interest to other scientists within the same field. Whereas in industry, there can be tangible results from the research in the form of new products or applications that have plans to be commercialized to benefit the public in some way. CRISPR biotechnology companies, including Caribou Biosciences and Editas Medicine, started out of academic institutions, where there is competition to commercialize CRISPR. So to explore the complexities of commercializing this technology, including the legal implications of this

[6] Brinegar, K., Yetisen, A. K., Choi, S., Vallillo, E., Ruiz-Esparza, G. U., Prabhakar, A. M., ... Yun, S. (2017). The commercialization of genome-editing technologies. *Critical Reviews in Biotechnology,* 1-12. doi:10.1080/07388551.2016.1271768

competition, my focus is to explore the commercialization of CRISPR originating from academic institutions.

CRISPR – The Duality of Molecular Scissors

CRISPR, "the disruptor," as a Nature article[7] labels this technology, is being applied across a variety of industries, from agriculture to animal disease models that aim to prevent and treat genetic diseases, such as sickle-cell anemia. The acronym CRISPR is short for Clustered Regularly Interspaced Short Palindromic Repeats, describing the organization of short, partially palindromic repeated DNA sequences that are unique and separated by random DNA sequences.[8] Among the excitement surrounding the growing number of CRISPR studies and publications from research labs around the world, it is easy to overlook this technology's origins.

CRISPR sequences stem from a natural process – they are an essential component of bacteria's immune defense system. In a bacterial cell, the CRISPR-based immune system works in three basic steps: 1) Adaptation – when a new virus attacks a bacterial cell, a part of the virus, a spacer, is derived and combined into the bacterial cell's CRISPR sequence. This step allows the bacterial cell to record the "memory" of the virus attacking. 2) Production of CRISPR RNA molecules – the CRISPR sequence with the newly incorporated viral DNA sequence is transcribed to produce molecules of CRISPR

[7] Ledford, H. (2015, June 08). CRISPR, the disruptor. Nature, 522(7554), 20-24. doi:10.1038/522020a

[8] Pak, E. CRISPR: A game-changing genetic engineering technique - Science in the News.

RNA. The CRISPR RNA matches the viral DNA sequence exactly. 3) Targeting – when the same type of virus attacks the bacterial cell in the future, then these CRISPR RNAs guide the bacterial cell's molecular machinery, a nuclease like Cas9, to the matching sequence in the invading virus so that Cas9 can identify, then cut, and ultimately destroy the virus.

See Figure 1 for the timeline of CRISPR events. The CRISPR story started in 1987, when researchers in Japan found a "series of repeated stretches…interrupted by unique 'spacer' sequences."[9] The mechanism was elucidated over the next 10 years as more repeating elements were observed in the genomes of different bacterial strains. In 2000, Mojica et al. classified the interspaced repeat sequences as a unique group of clustered repeat elements in bacteria, and not long after, in 2002, the CRISPR acronym was adopted.

Only recently, in 2012, did it become clear that the CRISPR technology can be applied in genome editing. Jennifer Doudna and Emmanuelle Charpentier realized that bacteria's CRISPR immune defense system has the potential to edit human genes or those of any other organism. In a *Science* paper published in June 2012, Doudna, an American RNA biologist, and Charpentier, a French microbiologist, showed site-specific DNA cleavage for the first time when using the Cas9 protein *in vitro*. They believe "the potential for CRISPR applications…will affect almost every aspect of life, and provide

[9] Fitzpatrick Dimond, P. F. (2013, November 8). CRISPR Madness.

inspiration for future technological breakthroughs."[10] Still, it wasn't until January 2013 when Feng Zhang, MIT bioengineer, developed a new version of CRISPR-Cas9 and directly performed gene editing in human cells.

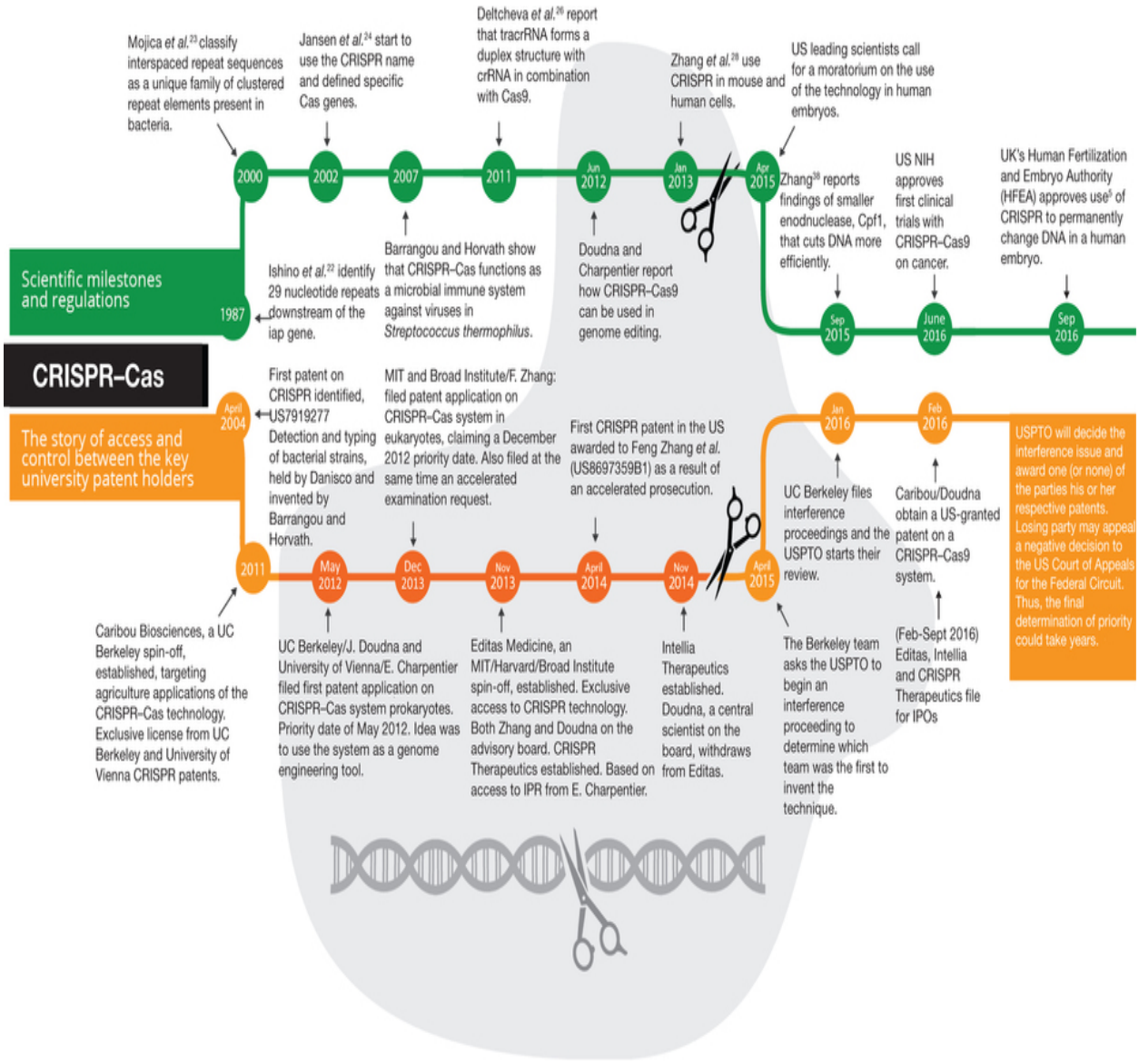

Figure 1 from *Nature Biotechnology* (2016) 34:1025

[10] Egelie, K. J., Graff, G. D., Strand, S. P., & Johansen, B. (2016, October). The emerging patent landscape of CRISPR-Cas gene editing technology.

In 2012, as more of the scientific community learned about CRISPR, this nascent technology was welcomed into labs around the world and researchers began to alter genes. In contrast to ZFNs and TALENs, CRISPR is considered to be easier and faster to use, more accessible, and cheaper.[7]

> "CRISPR is the Model T of genetics," says Hank Greely, a professor at Stanford Law School and the director of the Center for Law and the Biosciences. "The Model T wasn't the first car, but it changed the way we drive, work, and live. CRISPR has made a difficult process cheap and reliable. It's incredibly precise. But an important part of the history of molecular biology is the history of editing genes."[11]

CRISPR's introduction is gaining popularity in the realm of molecular biology; however, a tool that is easy to use is also one that is easy to abuse. The duality of the CRISPR technology is subtle but necessary to address when considering the complexities of this tool.

[11] Specter, M. (2015, November 16). The Gene Hackers.

Legal and Ethical Implications of CRISPR

In order to fully comprehend the significance of CRISPR's role in revolutionizing genome-editing technology's transition from academic research into commercialized products, I will focus on and deconstruct two main complexities. The first complexity concerns the legal implications I will explore through the question *how does the CRISPR patent dispute play a role in CRISPR's path to commercialization*, and the second complexity involves the ethical implications guided by the question of *what are the current ethical guidelines working with CRISPR*.

Legal Implications

The battle for exclusive scientific rights is not unusual among universities. In 1974, Stanford University and UCSF applied for a patent on Boyer and Cohen's development of recombinant DNA. The academic institutions received the patent in 1980. However, originally universities were unable to receive federal funding to develop their patented inventions. Once the Bayh-Dole Act of 1980 was passed, public universities could patent federally funded research. As more public research institutions began seeking patents for their discoveries, these institutions became more immersed in the commercialization of their research. Many institutions seek patents for their discoveries to gain exclusive rights to commercially use and exploit the invention for a

certain period of time, reducing competition from other institutions that also want to exploit that invention. Additionally, after receiving a patent, institutions have the power to sell or license the rights to others as a source of income.[12] The CRISPR patent dispute between UC Berkeley and the University of Vienna vs. the Broad Institute of MIT and Harvard University is the most recent and highly discussed example of leading research institutions competing for the rights to own and develop a genome-editing technology. This patent dispute exhibits how patents can influence the ethical implications of utilizing the CRISPR technology.

Doudna and Charpentier's 2012 paper revealed CRISPR's potential as a gene-editing tool, while Feng Zhang's 2013 paper demonstrated that he took Doudna and Charpentier's finding a step further with his direct application of CRISPR in human cells. Zhang ultimately demonstrated that CRISPR is an efficient way of editing any organism's genome. Both groups recognized the promising possibilities of their discoveries, and so UC Berkeley and the University of Vienna, the respective institutions that Doudna and Charpentier are affiliated with, and the Broad Institute at MIT and Harvard University, where Zhang is, filed patent applications for their work.

In late 2012, UC Berkeley and the University of Vienna filed a U.S. patent application through the U.S. Patent and Trademark Office (USPTO) together, while the Broad Institute at MIT and Harvard University filed their first patent application a few

[12] Reasons for Patenting Your Inventions.

months later. Although Doudna's team filed first, Zhang's team fast tracked their application. Consequently, in April 2014, the Broad Institute at MIT and Harvard University were granted U.S. patents. To counter this result, UC Berkeley filed an interference proceedings request to the USPTO in April 2015, providing the argument that Doudna and Charpentier were first to discover the aspects of CRISPR that were included in the granted patent to Zhang and his team at the Broad Institute and Harvard University.

In February 2017, judges at the USPTO confirmed that Zhang's work on living animal and plant cells was original work that deserved patent protection. So the USPTO ruled that Zhang, the Broad Institute, and Harvard University's patents concerning editing eukaryotic genomes with the CRISPR technology did not interfere with the claims UC Berkeley and the University of Vienna filed. The East Coast institutions were victorious in keeping their CRISPR patents – Zhang expressed relief that he could finally go back to focusing on his research.

Doudna and Charpentier still received patents on their original work on CRISPR. However, the patent outcome was based partly on Doudna's comments when she voiced her uncertainty about whether CRISPR would work in cells with nuclei – Doudna fears the patent ruling could make "every scientist now factor in a potential patenting strategy and alter how transparent [he is] about [his] work." [13] In other words, this ruling

[13] Achenback, J. (2017, February 17). CRISPR pioneer muses about long journey from China to pinnacle of American science.

could result in less transparency in scientific communication as scientists withhold information or mask their uncertainties in their research in order to attain patents.

Both parties of the patent dispute have created companies co-founded by their researchers: UC Berkeley and Doudna co-founded Caribou Biosciences and the Broad Institute at MIT and Zhang co-founded Editas Medicine. In addition to the financial investments in these biotechnology companies, the CRISPR patents are believed to be worth hundreds of millions, and possibly billions of dollars.[14] Commercial agreements with agricultural and biomedical companies are tied up with billions of dollars at stake. For example, DuPont Pioneer, a large seed producer for agriculture, and Caribou Biosciences have entered into a strategic alliance to use CRISPR with the same or fewer resources to produce higher-yielding crops, while Vertex Pharmaceuticals, a drug company, and CRISPR Therapeutics have entered into a $2.6 billion agreement to develop treatments for genetic diseases like sickle-cell anemia and cystic fibrosis.[15] Both parties of the dispute retained their patents, so companies that had entered into commercial agreements with either of the two parties face uncertainty regarding whether they have to attain licenses from both parties in order to utilize the CRISPR technology in eukaryotic cells.[16]

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[14] Sherkow, J. S. (2016, April 14). CRISPR: Pursuit of profit poisons collaboration. Nature, 532, 172-173. doi:10.1038/532172a

[15] CRISPR Commercialization Risk.

[16] Ledford H. (2017, February 23). Broad Institute wins bitter battle over CRISPR patents. Nature, 542, 401. doi:10.1038/nature.2017.21502

The bitter CRISPR patent dispute between Doudna's and Zhang's sides has been resolved, but going forward the verdict reveals complex questions about how scientists should communicate to others about their CRISPR research and the licensing steps companies need to take to use CRISPR in developing practical solutions for consumers.

Ethical Implications

Researchers have high hopes that the CRISPR technology can ameliorate many of the challenges that the life sciences face, from creating hardier plants to editing human genes in order to eliminate diseases. Although this genome-editing technology has a lot to offer, its safety and ethical concerns cannot be ignored. Researchers have been struggling to establish an ethical framework in regards to working with genome-editing technology ever since the 1970s. A possible explanation for this struggle is the vast number and complexity of ethical questions that emerge when a technology is introduced. When researchers do not fully understand the intricacies of the technology's mechanisms, we cannot anticipate all the applications and potential ramifications of utilizing it. Consequently, we are limited in our ability to address the large quantity of difficult ethical questions pertaining to the use of the genome-editing technology. Additionally, establishing an ethical framework involves taking individual interests and those of the community into consideration; however, the best outcome for one individual does not suggest that it is the best outcome for everyone. Still, by

grappling with the various difficult ethical questions, we can strive to implement ethical guidelines that account for everyone's best interests given the limitations in our knowledge of the genome-editing technology.

From interviews I conducted with CRISPR scientists at MD Anderson Cancer Center, I identified researchers' limited ethical awareness about the implications of their work. The limited ethical awareness is most likely the result of researchers' narrower scope of focus in better understanding the mechanical functions of a genome-editing technology. Researchers' work is highly technical, where researchers are immersed in the scientific process to learn more about the technology's mechanisms. Ethical questions about the application of a genome-editing technology tend to be outside the scope of the research lab, so researchers often do not have the time to focus on the ethical issues when researchers' priorities are more science driven. In a phone interview with Dr. Lei Li, a professor of cancer research who is conducting CRISPR research at MD Anderson, when asked what challenges there are in working with CRISPR, his response focused on the technical difficulties of using the technology. Only when I brought up the topic of social and ethical implications of using CRISPR did Dr. Li share that he had not considered the ethical implications before because all of his research and the research conducted at MD Anderson were within the National Institutes of Health guidelines, involving no embryo research.[17] Additionally, we are observing evolving attitudes

[17] Li, L. (2016, November 23). Interview with CRISPR Scientist [Telephone interview].

towards the science enterprise with the public's reticence to accept genome-editing practices, especially those involving germline editing,[18] in part due to scientists' failure to effectively communicate information about the technologies with nonscientists.

Human germline editing has become a deeply controversial topic when exploring ethical implications in the use of CRISPR technology. Germline editing involves altering genes that can be transmitted to future progeny. Proponents of human germline editing argue that it might decrease, or even eliminate, the incidence of genetic diseases and consequently diminish human suffering. However, most recently, this type of modification sparked unsettling concerns when Chinese researchers reported genome editing of human embryos to correct the gene mutations responsible for beta-thalassemia, a type of genetic blood disorder. The researchers' experiment was unsuccessful – only a small fraction of the CRISPR-edited cells in the embryos contained the corrected genetic material. *Nature Biotechnology* interviewed researchers, business leaders, and ethicists on the discussion of ethical issues of human germline engineering with CRISPR. Emmanuelle Charpentier's interview response emphasizes that safety concerns are potentially the most significant challenges to address.[19] Though she did not specify what those safety concerns are, based on context, Charpentier was most likely

[18] Human Genome Editing: Science, Ethics, and Governance. Rep. The National Academies Press, 2017. Web.

[19] Bosley, K. S., Botchan, M., Bredenoord, A. L., Carroll, D., Charo, R. A., Charpentier, E., ... Corn, J. (2015). CRISPR germline engineering - the community speaks. *Nature Biotechnology, 33*, 478-486. doi:10.1038/nbt.3227

referring to the premature use or misuse of CRISPR and the potential off-target effects of using this technology. Other researchers, business leaders, and ethicists also cited these same safety concerns in their interviews.

Off-target effects are not unique to CRISPR. There are varying levels of off-target activity depending on the target sequence that needs to be edited, but off-target effects caused by the use of CRISPR are "significantly lower" compared to those of other gene therapy strategies that use viral vectors.[20] Viral vectors are less precise, potentially randomly integrating into the genome to perform unintended edits. In contrast, CRISPR uses an engineered nuclease and precise RNA-guided system where the guide RNA "guides" the engineered nuclease to the target site in the genome where the engineered nuclease makes the intended edit. Despite CRISPR's relative precision, currently no genome-editing technology is completely error-free, including CRISPR, so off-target effects may still occur and affect other genes' functions, possible causing other unexpected diseases. In the case of the single-gene mutation that causes sickle-cell anemia, using CRISPR could cause off-target effects that, instead of correcting for that mutation, could lead to beta-thalassemia, another type of blood disorder.

After a group of Chinese researchers published their unsuccessful results with germline editing of human embryos using CRISPR in early 2015, the U.S. National Academy of Sciences, the U.S. National Academy of Medicine, the UK Royal Society, and

[20] *Ibid.*

the Chinese Academy of Sciences organized the International Summit on Human Gene Editing. In December 2015, nearly 500 ethicists, scientists, legal experts, and advocacy groups worldwide gathered in Washington D.C. for the summit. Thoughtful discussion on the prospect of human genome editing at this summit concluded with the organizing committee, composed of 12 physicians, bioethicists, and biologists, strongly endorsing the use of CRISPR in germline editing; however, they agreed that this application of CRISPR is currently "irresponsible because of ongoing safety concerns and a lack of societal consensus".[21] These ongoing safety concerns pertain specifically to off-target effects and although a consensus across societies seems unrealistic, since each nation has its own perspectives based on its respective cultural, social, and political situation, the international community should aim to create general guidelines. These general guidelines will then allow countries to create their own national regulatory policies that abide by those general guidelines. Establishing national regulations and norms about acceptable uses of genome-editing technologies can help to discourage unacceptable applications of these technologies.

This 2015 conference has been compared to the 1975 Asilomar Conference, where a group of approximately 140 participants, including scientists, lawyers, journalists, and government officials, had convened to discuss the technique and

[21] Travis, J. (2015, December 4). Inside the summit on human gene editing: A reporter's notebook.

implications of utilizing recombinant DNA.[22] Before the conference, scientists had called for a moratorium on recombinant DNA research, but at the conference, the moratorium was relaxed – it was decided that after assigning a risk estimate to each type of lab experiment that could be conducted with recombinant DNA, labs could better ensure lab safety while using this technology. As a result, recombinant DNA research in labs continued. The 1975 conference on recombinant DNA opened the discussion about science policy, just as the 2015 summit did, yet some people argue that the Asilomar conference was distinct.

David Baltimore, who was present at the Asilomar conference and was chair of the organizing committee at the summit on gene-editing, highlighted the difference between the Asilomar conference and the summit on human gene editing. Biosafety concerns about lab experiments using recombinant DNA motivated the 1975 conference, whereas ethical concerns about the safety of utilizing CRISPR in treating humans motivated the 2015 summit.[22] The current issues with genome-editing introduce more heterogeneous concerns that extend beyond questions on safe lab use of genome-editing technologies. Especially since CRISPR is the most advanced genome-editing technology we know of and is touted to be faster, cheaper, and easier to use compared to zinc-finger nucleases (ZFNs) and transcription activator-like effector

[22] Berg, P. (2008, September 17). Meetings that changed the world: Asilomar 1975: DNA modification secured.

nucleases (TALENs), heterogeneous concerns include questions about the scope of application of these technologies and who can benefit from those applications, for example.

In early 2017, the National Academy of Sciences published an updated ethics report on the use of genome-editing technologies, specifically discussing CRISPR.[23] This new report expresses a more permissive position towards germline editing – it suggests proceeding with caution but not entirely prohibiting germline editing to potentially treat certain rare diseases. There is slightly more leniency towards the use of CRISPR in this new report compared to the 2015 summit decision where the organizing committee believed it would be irresponsible to go forward with germline editing at the present time.[24]

The extensive ethics report from the National Academy of Sciences provides current ethical guidelines for genome editing in basic science lab research, clinical uses of somatic cell editing, and germline editing. Establishing ethical guidelines on the use of genome-editing technology like CRISPR is not a simple task. These ethical guidelines support us in making decisions that uphold the standards of behavior within a given society. Different countries have varying opinions of what constitutes "right" and

[23] Human Genome Editing: Science, Ethics, and Governance. (2017).
[24] Achenbach, J. (2017, February 14). Ethicists advise caution in applying CRISPR gene editing to humans.

"wrong" behavior, significantly influenced by each country's cultural, social, and political background. Even within the U.S., the diversity of stakeholders, comprised of scientists, business professionals, the general public, inter alia, means there are a variety of goals the stakeholders have that ethical guidelines should aim to address. For example, scientists aim to analyze the patterns from genetic data and animal models to better understand and discover more about the mechanisms of genome-editing technologies. Business professionals strive to invest in genome-editing technologies that have an economic incentive to be commercialized or to use and develop applications for consumers within healthcare or agriculture, for instance. Attempting to use a standard set of ethical guidelines to help all stakeholders achieve their personal goals is not a realistic task, but we can endeavor to identify general guidelines that support the harmonization of stakeholders' values and goals.

One way to approach developing these guidelines is to draw upon ethical principles that are often based on philosophical theories – for instance, deontologists may view some acts as always wrong, even if the outcome is beneficial. From a deontological standpoint, if the act of killing and editing a human embryo is wrong, even if the act could mean future prevention of more embryo deaths, there would not be a justification for editing the embryo. Utilitarians, on the other hand, evaluate whether the outcome is beneficial but may disagree on evaluating the consequences of a specific act. Therefore, a utilitarian perspective on the embryo editing example would favor

killing and editing an embryo for research because this act might help prevent a greater number of embryo deaths in the future. These two philosophical theories are just a few of the models that are taken into consideration in an effort to understand what standards of behavior are considered ethical. Public policy enacted to address the ethical use of genome-editing technologies does not draw upon philosophical theories necessarily. However, these theories can present to us the potential options we have when making ethical decisions in situations when we may utilize these technologies, for example in germline editing or in genetically-modified organisms (GMOs).

Beyond analyzing individual philosophical theories, there should also be a focus on approaching the ethical guidelines with "reflective equilibrium,"[25] a concept American philosopher John Rawls coined. Reflective equilibrium gathers a wide range of theories or beliefs about an issue and involves reflecting on and revising those beliefs in order to find a general coherence and understanding among the comprehensiveness of the beliefs. We undergo this period of reflection and revision of beliefs, testing them against each other, until they are not in conflict anymore and may support each other. Once our beliefs are not in conflict anymore, or are in equilibrium, then we can judge that our beliefs are morally sound, and consequently we are more likely to adhere to them.

[25] Daniels, N. (2003, April 28). Reflective Equilibrium.

In applying the model of "reflective equilibrium" with respect to CRISPR, we would first need to include both scientists and nonscientists in a discussion about the use of CRISPR. With both groups present to share their thoughts, we can identify various issues and beliefs about using CRISPR in genome editing. Take for example, the issue of germline editing using CRISPR. Some scientists may believe using CRISPR in germline editing is inevitable, while some individuals from the nonscientific group may be weary of using CRISPR in germline editing because of the fear of off-target effects. The groups would discuss their beliefs and test them out to determine if there is a way in which both beliefs can work together instead of being in conflict with each another. The discussion may revise individuals' original beliefs on germline editing or new concerns may surface. This process of reflection and revision of beliefs may yield a potential option that allows the two beliefs to work together: contingent on certain regulations, such as decreasing the risks of off-target effects to a safely determined level, proceed cautiously with using CRISPR in germline editing. With the two groups' beliefs working together to form this general consensus, there's a higher likelihood that both groups would comply to this option. Although identifying a coherent, general consensus may not be possible with every issue regarding the use of CRISPR, "reflective equilibrium" can at least help to identify the overarching issues that people have about using CRISPR and help to narrow down the potential options for next steps. We still do not

understand all the mechanisms of CRISPR yet, so the ethical guidelines need to be able to respond and adapt to new discoveries about this technology.

After exploring the legal and ethical complexities of CRISPR in this chapter, the next step is to examine the application of this technology in sickle-cell anemia and how the case reflects the complexities discussed in this chapter.

CRISPR in Sickle-Cell Anemia Case Study

Background on Sickle-Cell Anemia

Approximately 250,000 children around the world are born with sickle-cell anemia every year.[26] This disorder is particularly prevalent in African Americans and those with African ancestry and is the most common and often most severe kind of sickle-cell disease. Sickle-cell anemia is a recessively inherited blood disorder caused by a single DNA letter genetic mutation that leads to the production of abnormal hemoglobin, resulting in the characteristic "C" or "sickle"-shaped red blood cells (RBCs).[27,28]

Hemoglobin is found in RBCs, and it is the protein that carries oxygen in the lungs to all other body tissues. Healthy RBCs are round, flexible, and they easily pass through small blood vessels to deliver oxygen to organs and limbs. Our bone marrow makes RBCs, which typically live 90 to 120 days before dying, and the bone marrow replenishes those RBCs by producing a new supply.

In contrast, "sickle"-shaped RBCs are rigid, so it is more difficult for sickled RBCs to pass through the blood vessels compared to normal RBCs. As a result, sickled RBCs

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[26] Ledford, H. (2016). CRISPR deployed to combat sickle-cell anemia. *Nature*. doi:10.1038/nature.2016.20782

[27] Dewitt, M. A., Magis, W., Bray, N. L., Wang, T., Berman, J. R., Urbinati, F., ... Corn, J. E. (2016). Selection-free genome editing of the sickle mutation in human adult hematopoietic stem/progenitor cells. *Science Translational Medicine, 8*(360). doi:10.1126/scitranslmed.aaf9336

[28] Sickle Cell Anemia. (2014, December 16).

can block blood flow in the blood vessels leading to the organs and limbs, preventing oxygen from reaching the body tissues. This obstruction of blood flow can consequently lead to organ damage, severe pain, and also increase the risk for infections.[29,30] In addition to the disorder's distinctive "sickle"-shaped RBCs, the abnormal sickle cells usually only live for about 10 to 20 days. With abnormal sickle cells' much shorter life span, the body's bone marrow is unable to produce new RBCs at the speed needed to replace the dying RBCs. Consequently, another defining characteristic of sickle-cell anemia is the abnormally low number of RBCs in the body than the amount that is normally needed to deliver oxygen efficiently to the rest of the body.

Because sickle-cell anemia is an inherited blood disorder, a child can have sickle-cell anemia if either of the two situations occurs: both of the child's parents have sickle-cell anemia, meaning each parent has two sickle-cell genes, or if both of the parents have the sickle-cell trait, then each parent has only one sickle-cell gene. Inheriting two sickle-cell genes, one from each parent, causes the child to have sickle-cell anemia. After inheriting this disorder, different individuals experience varying severities of the disease; however, sickle-cell anemia is a life-long illness.

Currently some of the treatments to alleviate the symptoms of sickle-cell anemia include blood transfusions, antibiotics, and pain medications. Those with sickle-cell

[29] What is Sickle Cell Disease?
[30] What is Sickle Cell Anaemia? (2014, July 8).

anemia have weakened immune systems and thus, they are more susceptible to infections. Taking antibiotics can help to reduce the risk of getting infections. The only potential cure is a bone marrow transplant, but this route raises challenges: it is not widely available, the procedure is highly risky, and locating a genetically-matched donor is difficult.[31] Despite recent improvements in screening and treatment options, sickle-cell anemia is still not easily treated because a bone marrow transplant is highly dangerous and painful. Scientists are hopeful that utilizing a gene-editing solution like CRISPR will allow people to be their own bone marrow donors to reduce the risks associated with transplants.[32]

Sickle-Cell Anemia Case Study

[31] Sickle Cell Anemia. (2016, December 29).
[32] Cross, R. (2016, October 12). CRISPR edits sickle cell mutation. *Chemical & Engineering News*, *94*(41).

The Innovative Genomics Initiative is a UC Berkeley and UC San Francisco joint effort that aims to use CRISPR to correct DNA mutations that underlie human disease.[33] Contributing to that effort, in a sickle-cell disease study published in October 2016 of the online journal *Science Translational Research*, researchers from UC Berkeley, UC San Francisco Benioff Children's Hospital Oakland Research Institute (CHORI), and the University of Utah School of Medicine utilized CRISPR to correct the single-gene mutation responsible for sickle-cell disease in hematopoietic stem cells that were isolated from the blood of affected patients.[27,33] Hematopoietic stem cells are precursor cells that eventually mature into RBCs.

The multi-institutional team's main goal in this study was to produce healthy new RBCs using gene-editing methods to fix the mutation in patients' own stem cells. Of the approximately 1 million cells that were injected into the bone marrow of seven mice, 12% of those stem cells had been altered with CRISPR. Four months later, the scientists found an average of 2.3% of the genetically-engineered stem cells in the mice retained the edited DNA in their bone marrow. This 2.3% level of correction is an important advancement because the researchers believe the proportion may be high enough to produce a substantial clinical benefit in sickle-cell patients, though the efficiency of the process will need to be improved for practical use. Experts believe 5% - 10% of

[33] Sanders, R. (2016, October 12). Genome engineering paves way for sickle cell cure.

corrected mutations to develop healthy RBCs would be enough to cure sickle cell.[34,35] In contrast, the rate of editing the sickle-cell mutation using other gene-editing approaches was less than one percent.[36] Since the CRISPR-edited stem cells persisted after the transplant into the mice, there could be a potential long-lasting therapy based on this approach.[33]

Mark DeWitt, a researcher with the UC Berkeley Innovative Genomics Initiative, said that the team's next goal with the mouse study is to increase the percentage of altered cells that are present in the bone marrow from 2% to 5% after four months.[34] In addition, the study's researchers emphasize that the next steps for future pre-clinical work will involve continued optimization, larger-scale mouse studies, as well as meticulous safety analysis. The study involved injecting mice with about one million CRISPR-edited cells, but to conduct the study in humans, researchers would need to edit hundreds of millions of cells by scaling up the ability to edit genes. There are also safety concerns with utilizing CRISPR regarding off-target effects: "some of the inadvertent DNA changes could cause other serious diseases".[35] For example, using CRISPR to treat sickle cell disease could instead lead to a mutation in the gene that causes another serious condition called beta thalassemia, a blood disorder that reduces hemoglobin

[34] Netburn, D. (2016, October 12). With CRISPR, scientists correct genetic mutation that causes sickle cell disease.
[35] Begley, S. (2016, October 12). A CRISPR-based fix for human sickle cells shows promise in mice.

production. Consequently, the researchers aim to expand their study to include more lab animals to demonstrate that CRISPR-editing blood-forming cells is reasonably safe.

Biotechnology companies are becoming actively interested in using CRISPR to develop new treatments for sickle-cell disease. Biotechnology companies are major players in the commercialization of gene-editing technology. In October 2015 two biotechnology companies, Vertex Pharmaceuticals and CRISPR Therapeutics, entered into a four-year strategic research collaboration to use the CRISPR technology to discover and develop potential new treatments targeting the genetic causes of human disease. One of the two companies' initial focuses is to discover treatments to address the known genes and mutations that contribute to and cause sickle-cell disease.[37]

[37] Vertex and CRISPR Therapeutics Establish Collaboration to Use CRISPR-Cas9 Gene Editing Technology to Discover and Develop New Treatments for Genetic Diseases. (2015, October 26).

Antisense Technology in Flavr Savr Tomato Case Study

In the 1990s, the Flavr Savr tomato became the first commercialized genetically engineered food product. This crop product's journey from the lab to the market exemplifies the challenges faced at the intersection of science, business, and social perceptions. First Fruit: The Creation of the Flavr Savr Tomato and the Birth of Genetically Engineered Food, written by Belinda Martineau, one of the researchers who developed the Flavr Savr tomato, details the tomato's journey from successfully being the first commercially sold, genetically engineered whole food through the time of its eventual demise. With the aid of Martineau's book, I outline and discuss the main events of the Flavr Savr tomato case study in order to establish a foundation for comparison to the sickle-cell anemia CRISPR case study explored in the previous chapter.

In early 1988, Calgene, Inc., an independent agricultural biotechnology company in Davis, California, was growing tomato plants that contained the antisense polygalacturonase (PG) gene. However, at the time, Calgene did not plan to establish the tomato as a potential commercial opportunity. Instead, the focus was on developing the company's herbicide-resistance program and the BromoTol gene, which could help crop plants resist an herbicide that would typically kill them. Within a few months, though, a significant discovery from a scientific experiment involving the tomatoes

growing at Calgene marked a turnaround in the company's interests in the agricultural biotechnology industry.

In the scientific experiment, Calgene scientists had two different groups of tomato plants: one group had the genetically inserted Flavr Savr tomato gene that utilized "antisense technology" and the other group was nonengineered. Tomatoes were harvested from the genetically engineered tomato plants and from the nonengineered tomato plants – these harvested tomatoes were kept at room temperature and observed over time. In three to four weeks, the tomatoes with the antisense PG gene still looked and felt as if they were freshly picked, whereas the non GMO tomatoes were shriveled and rotting. The stark difference between these two groups demonstrated that the tomatoes with the antisense PG gene had a dramatically longer shelf life than that of ordinary tomatoes. This promising observation began to garner the attention of Calgene's management to use the antisense PG gene as a potential business prospect in tomatoes.

A persistent issue the tomato industry had been facing was trying to provide fresh-market tomatoes to consumers. For the fresh market tomato industry, it was essential for tomatoes to survive shipment to markets. Calgene aimed to change the fresh tomato business with the observations from its experiment: the company wanted to position the Flavr Savr tomatoes as the epitome of vine-ripened, high-quality tomatoes.

The issue fresh-tomato businesses faced was that when non-GMO tomatoes reached grocery stores they would soften and rot on the shelf before they could be sold. Plant breeders worked for decades to toughen and improve tomatoes' shippability. Traditionally, one solution to address this problem was to pick the tomatoes when they were still unripe, firm to the touch and completely green. When these tomatoes were hard and green, they could survive the transport to distributors and grocery stores, where ethylene gas was used to artificially ripen the tomatoes. However, even though the "gassed" tomatoes looked red and ripe, they did not attain the full flavor that vine-ripened tomatoes possessed. American consumers expressed dissatisfaction with the taste of artificially-ripened tomatoes. Although American consumers complained about the taste of fresh tomatoes, each American consumer purchased an average of 17 pounds of fresh tomatoes every year.

From the Calgene tomato experiment, scientists concluded that a second and potentially more effective solution than gassing green tomatoes involved eliminating the PG protein in the tomato fruit by expressing an antisense PG gene to construct the Flavr Savr tomato. Scientists could then extend ripe tomatoes' shelf life so that customers would buy the tomatoes before they displayed signs of rotting or damage, and the antisense PG gene might even help improve the taste of the tomatoes. With the $4 billion fresh tomato market, introducing Flavr Savr tomatoes seemed to be a compelling solution to the fresh market tomatoes problem. Not only would consumers

buy more tomatoes, but also the company predicted consumers would be willing to pay more in exchange for enjoying more flavorful tomatoes.

To more clearly understand antisense technology's role in gene editing, it is important to understand the basic mechanism of how proteins are formed in two steps: transcription and then translation. In the first step, the genetic code of a gene is transcribed into mRNA, and then the mRNA travels to the ribosomes, where the second step occurs. In the second step, the mRNA serves as a set of instructions for the ribosomes to translate the mRNA's genetic code into amino acids, which are the building blocks of proteins. See Figure 2.

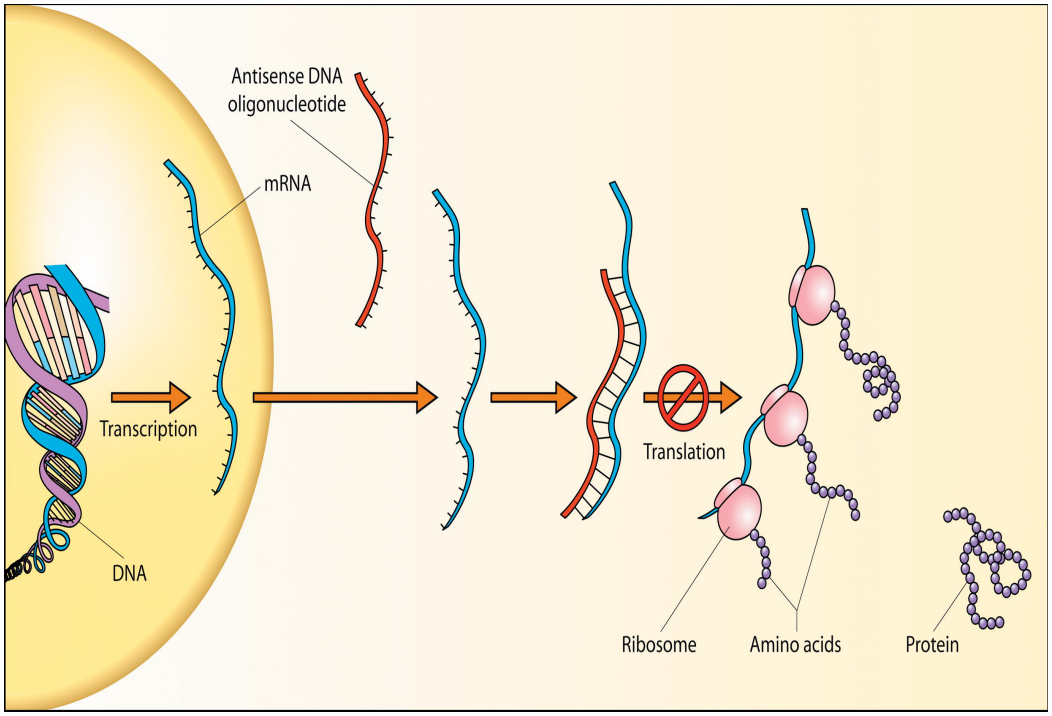

Figure 2 from Antisense DNA Oligonucleotide by Robinson R [CC BY 2.5 (http://creativecommons.org/licenses/by/2.5)], via Wikimedia Commons

Antisense technology is able to silence a gene's effect by inhibiting the translation step. This tool aims to silence, or turn off, a gene's effect, instead of correcting a mutated gene.[38] The term "antisense" describes the sequence that is complementary to the DNA or RNA sequence while "sense" refers to the original DNA or RNA sequence. The general principle behind antisense technology involves base pairing an antisense nucleic acid sequence with its complementary sense RNA sequence – the cell will not recognize the double helix, and so, the cell will proceed to degrade the faulty RNA sequence. With a degraded RNA, the cell does not have a sequence to translate, and consequently, the cell is not able to build the protein.

Researchers capitalized on this naturally occurring process to develop antisense technology as a gene-editing tool to provide the instructions to inhibit gene expression and prevent protein formation in tomatoes. The antisense PG gene that the researchers co-opted for use in tomatoes comprised of a copy of a tomato fruit gene that coded for polygalacturonase (PG), an enzyme that is involved in fruit ripening. The PG gene in non GMO tomatoes and the engineered antisense PG gene differed in one primary way: the engineered gene was flipped upside down and backward, resulting in the antisense PG gene. This antisense PG gene was capable of shutting down the natural process of PG

[38] Liou, S. (2010, June 29). Antisense Gene Therapy.

protein production in the tomatoes, thereby slowing down the process of fruit ripening.

See Figure 3.

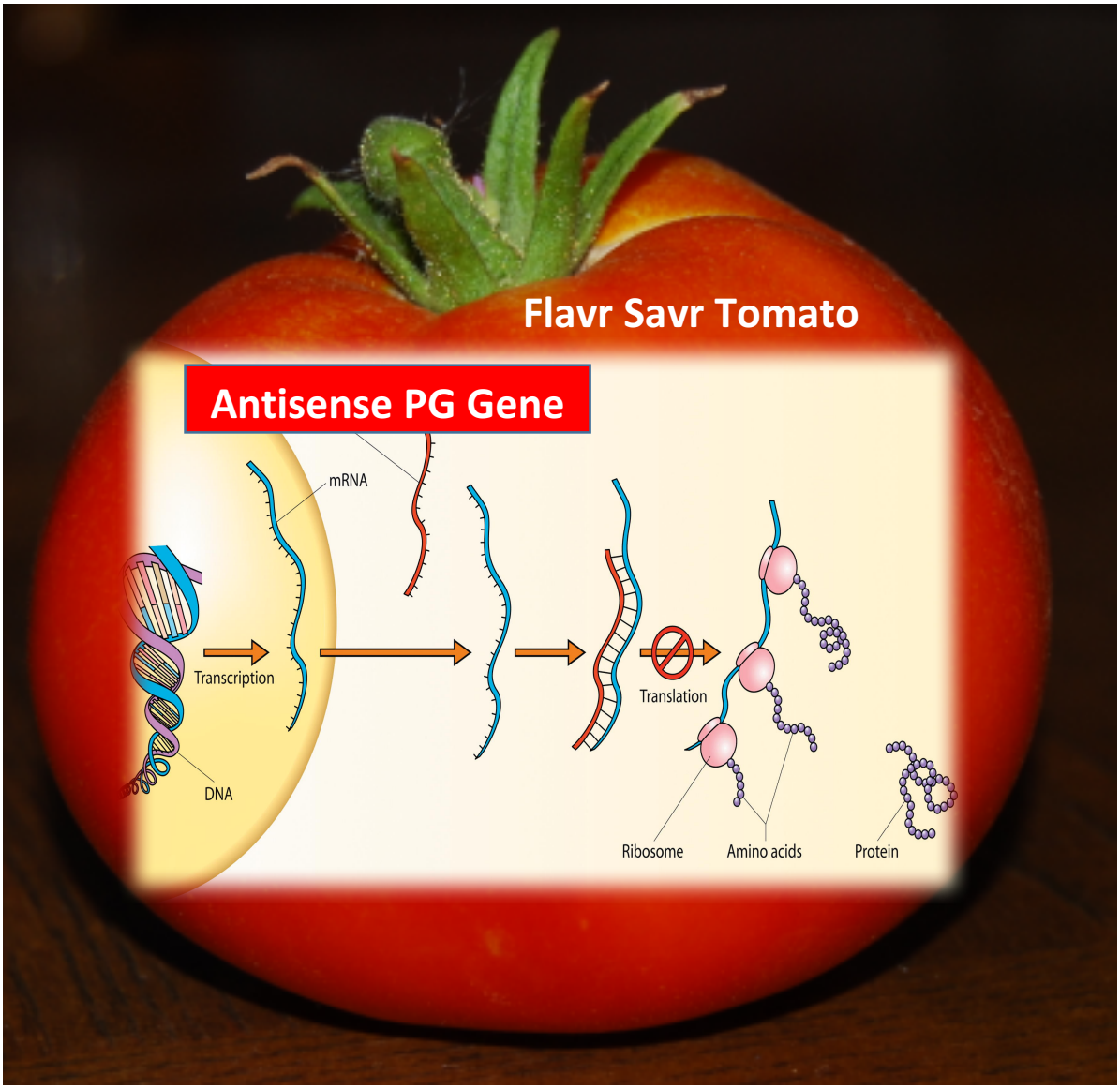

Figure 3 adapted from Antisense DNA Oligonucleotide by Robinson R [CC BY 2.5 (http://creativecommons.org/licenses/by/2.5)], via Wikimedia Commons

Calgene scientists understood the process by which the antisense PG gene shut down PG production in the genetically-engineered tomatoes. However, many of the scientists, including William (Bill) Hiatt who was the head scientist in charge of Calgene tomato research was hesitant to publish the preliminary observations based on this one experiment. When the media heard about the Calgene experiment's results, news reporters eagerly wanted to cover the story about the potential for longer-lived tomatoes. Calgene scientists, though, deferred from talking to the press, because they were not confident about the validity of the experiment's results. After additional testing, scientists found that Flavr Savr tomatoes ripened normally, but that PG activity had a more dominant role in the deterioration of the tomato during the overripe stage of ripening. What was the advantage for a fresh-market tomato business if these genetically-modified tomatoes still underwent the initial process of fruit softening normally? On the other hand, those who were part of Calgene's business planning effort decided to make an extrapolation of the Flavr Savr tomato shelf-life phenomenon, inventing this product and outlining the company's positioning for commercializing vine-ripened, high-quality tomatoes.

Calgene believed that consumers' appeal for tasty, vine-ripe tomatoes was enough to offset consumers' wariness of the antisense technology used in Flavr Savr tomatoes. The company hoped that since the technology introduced a genetically modified piece of DNA that contained an antisense gene from the same organism, it

would help ease consumer acceptance of the Flavr Savr tomato, as well as help increase the chance of successfully attaining approval for commercializing the product from U.S. regulatory agencies.

Legal Challenges – Patent Interference

In 1992, the U.S. Patent Office issued a patent to Calgene for the use of antisense technology to shut off any gene in any plant cell. Though it appeared that Calgene's use of this technology was protected, Calgene was not the only one who was issued antisense patents. The State University of New York was issued three broad antisense patents, and then it exclusively licensed those patents to Enzo Biochem, Inc. What ensued were suits and countersuits from both Calgene and Enzo alleging patent infringement, patent invalidity, and unfair competition. In one suit, Enzo alleged that Calgene committed willful patent infringement. All of Calgene's employees, about 150 at the time, had to turn in documents and notebooks that had any mention of the use of antisense technology – this perusal found that of the over 2,300 lab notebooks half of them contained work related to antisense technology. In 1993, it was already widely known that Calgene was utilizing antisense technology; Calgene scientists felt that the time and effort invested in investigating all the documents and notebooks was a waste of time. Instead, scientists believed the focus should have been on establishing the

validity of Calgene's antisense patents rather than addressing Enzo's infringement claims.

In 1995, the Enzo patent case went to trial. The trial centered on four main patent issues: *enablement*, *inequitable conduct*, *obviousness*, and *prior art*. In the first issue of enablement, although Masayori Inouye at the State University of New York, who was issued the three broad antisense patents and later licensed them to Enzo Biochem, Inc., did perform the antisense work before Calgene, Calgene claimed that Inouye did not "sufficiently [enable] someone skilled in the art to use the invention in plants" (209). Inouye antisensed three different genes; however, they were in *E. coli*, the bacteria. Calgene argued that his work with antisense technology in a bacterial cell did not demonstrate that the technology could work in a plant cell. The second issue of inequitable conduct surfaced when Inouye neglected to disclose to the USPTO about the other cellular systems he had taken that did not succeed. The third issue of obviousness involved Enzo's claim that after Inouye's antisense results in *E. coli*, utilizing antisense in plants was a logical next step. Therefore, Enzo argued that the USPTO should not have issued the antisense patent to Calgene from the start.

The fourth and last patent issue of the trial involved prior art. Calgene previously cited published research conducted at Harold Weintraub's lab at the Fred Hutchinson Cancer Research Center in Seattle in its original patent application, so the question was whether Inouye's antisense work came before the research conducted at the cancer

research center on a calendar basis. Calgene obtained a nonexclusive license to Weintraub's own antisense patent application. If Weintraub's work was first, then based on prior art Inouye's work may be seen as obvious. However, the biggest controversy in the entire case that related to the prior art issue was that Enzo claimed that Weintraub's lab engaged in scientific misconduct when preparing to publish the antisense work. To investigate this allegation, Enzo brought in Walter Gilbert, the Nobel laureate from Harvard. He concluded that there was manipulation of the data to make it appear extremely accurate. To counter these claims, the Fred Hutchinson Cancer Research Center responded by conducting an internal investigation and found that Gilbert's allegation was without merit.

From Calgene's perspective, the *Wall Street Journal* increased the company's troubles when the *Journal* published an article that had incorrect information, stating that Calgene was attempting to attain a patent for the antisense technology, when in fact, Calgene had already been issued its antisense patent three years ago. Additionally, the article stated that "[Calgene] losing the case might delay [its] nationwide rollout of the Flavr Savr…and jeopardize its stated plans to become profitable in 1996" (211), causing Calgene to question the *Journal's* intentions. Calgene's CEO Roger Salquist responded to the article and said that the outcome of the patent trial would not impact the rollout of Calgene's Flavr Savr tomatoes; fortunately, the *Journal* immediately printed a corrected version of the article the following day. In 1996, the Enzo patent

decision came out – U.S. District Court Judge Joseph J. Farnan ruled Enzo's antisense patents invalid and upheld Calgene's antisense patent, so there was no need to address whether Calgene had infringed on Enzo's patents. Later in 1999, the federal appeals courts decided to only rule parts of two of Enzo's three antisense patents were invalid, limiting the district court's judgment in 1996 of the invalidity of Enzo's antisense patents.

Clash Between the Science and Business Cultures at Calgene

The inception of this new fresh tomato project naturally brought the business and science sides of Calgene together, introducing conflicts of interest. A kind of "culture shock" was injected into the company. Calgene's business executives were excited about the potential business opportunity of developing and commercializing tomatoes that could be ripened while still on the vine and yet still maintain the firmness necessary to endure the shipment process. The business staff believed that further testing was the only obstacle standing between the perception and the reality of tastier, higher-quality fresh tomatoes. Calgene scientists, however, were less optimistic about the Flavr Savr tomato – there was experimental evidence supporting the possibility of a tomato with a longer shelf life, but scientists did not have data supporting the claim that a vine-ripened tomato could endure the journey to grocery stores. Without empirically-

derived evidence supporting the hypothesis, the scientists feared that the fresh tomato Calgene business executives hoped to develop would not become a reality.

With the introduction of the Flavr Savr tomato project, Calgene's business impact on its science was apparent when layoffs among the science staff occurred in 1988, only the second occurrence of layoffs in the company's history. Business executives explained that high R&D spending caused the financial losses in 1988 that resulted in the layoffs. However, the report to shareholders indicated that Calgene's management team had failed to reach its financial targets, yet the science staff had to pay for it. How Calgene would approach its business strategy with the new Flavr Savr tomato project was another source of disagreement between Calgene's business executives and scientists.

Calgene's management team wanted to invest in a vertical integration strategy, building up several different businesses in order to generate the kind of money that only vertical integration could supply. But rather than investing in multiple businesses or products, some Calgene scientists were more supportive of a "gene boutique" where they believed Calgene should continue doing what it did best: cloning genes, transferring the genes to and expressing them in plants, and ultimately selling or licensing those cloned genes to agricultural businesses. Calgene scientists understood that in order for Calgene to survive, the company needed to make money; however,

there were still conflicts of interest between management and the science staff that led to many of the challenges contributing to Calgene's demise.

One of the first impacts to Calgene's transition to business mode involved the creation of Calgene Fresh, Inc., a subsidiary of Calgene that served as the company's marketing arm but had a separate management team and kept its own books for business purposes. Establishing Calgene Fresh meant that Calgene would be undergoing a reorganization: Calgene tomato scientists would be consolidated into one lab. Prior to the introduction of the Flavr Savr tomato idea, Calgene scientists were largely left to their own devices and found throughout the company's labs. The scientists enjoyed scientific independence as well as the opportunity to integrate and collaborate with other scientists who were working on different projects: there was the sharing of ideas, materials, successes, and failures. Calgene's management believed that bookkeeping would be simpler if the scientists working on the Flavr Savr tomatoes were segregated from the other Calgene scientists. In contrast, the scientists thought that easier bookkeeping was not an adequate reason to segregate the tomato scientists from everyone else. Rather, the scientists knew that it would take some time to adjust to the new lab environment at Calgene Fresh, and during that time their research efficiency would significantly be reduced. Additionally, the reorganization and segregation of the scientists introduced the possibility for internal strife among the scientists: there were questions about whether the tomato group would receive preferential treatment,

better lab space, inter alia? These questions began to erode the strong scientific community at Calgene.

Once Calgene Fresh was created, Salquist believed that Thomas Churchwell, who was a member of Calgene's board of directors and had sales expertise, would be a great choice as the president and CEO of this subsidiary. However, it was clear to the scientists that Churchwell was not fit to lead Calgene Fresh and market the Flavr Savr tomato to success. Scientists believed he made decisions that did not make sense – for example, he chose to move Calgene Fresh's central offices to Evanston, Illinois, as far away as possible from major fresh tomato growing centers in California and Florida. There were three key issues between the business and science staff that contributed to Calgene's demise: the lack of communication, the culture clash between management and scientists, and the lack of business expertise.

The first issue was the lack of clear communication between management and scientists. Churchwell expounded his plan to develop a new corporate culture at Calgene Fresh, one that upheld open communication among all employees. Although the scientists respected Churchwell's sincerity in his visions for Calgene Fresh, the scientists felt that Calgene's corporate culture already reflected the open communication and collaboration that he was envisioning. However, from the scientists' interactions with Churchwell, his use of circumlocution in his manner of communication caused the scientists to believe that that way of speaking was common in business.

Churchwell's confusing, indirect communication elicited doubts among the scientists that he would be able to facilitate effective communication at Calgene Fresh.

The second issue involved the clash of business and science cultures. As part of developing a new corporate culture, Churchwell created organizational vision meetings that focused on establishing Calgene Fresh's core values and beliefs, defining quality, and most importantly on integrating the scientists into the business and creating a common culture and language. Still, the scientists at Calgene Fresh preferred to discuss scientific plans and their results rather than the organizational decisions around them.

The business and science staff not understanding one another's values and practices created another source of contention between the two. The business staff wanted concrete numbers and definite answers from experiments; however, the scientists explained that there were chances where scientific experiments may not demonstrate identifiable correlations. Scientists were surprised that even after several years working at Calgene the business staff still did not understand the basic definition of an experiment.

Lack of Sufficient Business Expertise

Calgene Fresh did not understand agriculture, what tomato varieties to grow, nor how to handle the fruit – there was an evident lack of sufficient business knowledge in managing the tomato business. There were two anecdotes that clearly portray the consequences of this issue.

When Churchwell was appointed to head Calgene fresh, the Calgene board of directors told him, “The good news is that you know nothing about the tomato business so you won’t fall into the old traps that [others] have. The bad news is that you know nothing about the tomato business and you’ll fall into traps that they know how to avoid” (136). With this insight, Churchwell knew he had to establish partnerships who were committed to fresh quality and could supply Calgene Fresh with a large amount of tomatoes. Calgene Fresh was on a steep tomato market learning curve.

In one anecdote, Calgene’s marketing strategy in promoting the Flavr Savr tomatoes in grocery stores was unsuccessful. Not long after Calgene started selling the Flavr Savr tomatoes, the number of damaged, unusable tomatoes, or shrink, was as high as 50% of the available tomatoes and had to be thrown away. To address this issue, Calgene Fresh created a sales incentive program where it agreed to repurchase fruits a grocery store did not sell, in order to attain retail space for Flavr Savr tomatoes. However, this strategy only continued to increase shrink levels, making it much more

expensive and challenging to provide consistently flavorful and superior texture Flavr Savr tomatoes to consumers.

The second anecdote portrays Calgene's lack of knowledge about the best places to grow tomatoes and tomato handling techniques. To help increase the quality of the tomatoes, and consequently decrease the shrink levels and costs Calgene strategically turned to the help of experienced tomato grower-shipper partnerships. Calgene Fresh successfully executed deals with three tomato suppliers and had a growing location in Mexico, which could help produce a year-round supply of tomatoes. However, Mexico tomato shipping tests were disappointing. Flavr Savr tomatoes that traveled by truck from Mexico to Chicago would be damaged along the journey, causing high expenses due to the loss of tomato supply. This was only the beginning of Calgene Fresh's honing of tomato shoveling over the next few years.

Comparative Case Analysis
CRISPR in Sickle-Cell Anemia and Antisense in Flavr Savr Tomatoes

Genome-editing technology, such as CRISPR and antisense technology, are just two of the genetic tools researchers utilize to study genomes and to investigate the effects of altering genes. The application of antisense technology in Flavr Savr tomatoes occurred in the late 1980s while CRISPR's application in sickle-cell anemia is currently in progress. In this section, I will conduct a comparative analysis of these two case studies, using the lessons learned from the Flavr Savr tomatoes case as a "lens" through which to view the use of CRISPR in the sickle-cell anemia case. I will consider the use of CRISPR and its path to commercialization in three areas: legal implications, ethical implications, and the convergence of science and business. By considering the impact of CRISPR technology in these three areas, guidelines and recommendations can be implemented to support future applications and commercialization of CRISPR.

Legal Implications

The antisense technology patent dispute between Calgene and Enzo was less contentious compared to the CRISPR patent dispute between Jennifer Doudna's and Feng Zhang's teams. Before Calgene adopted antisense technology to create the Flavr Savr tomato, companies did not have experience using antisense technology to maintain a tomato's ripeness from the vine to the store while also guaranteeing a flavorful taste.

All the potential applications of this technology were still being explored in the 1980s, so the most well-known application of antisense technology was in the Flavr Savr tomato.

Genome-editing technologies have been evolving to embrace more sophisticated, advanced characteristics. For example, both zinc-finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) both use a non-specific nuclease to cut the target sequence, but CRISPR demonstrates a simpler, more precise target mechanism. CRISPR does not rely on DNA recognition of the target sequence to edit the genome, so guide RNAs can be easily and cheaply designed to target almost any sequence in the genome specifically.[39]

Since CRISPR's discovery and the beginning of the CRISPR patent dispute in 2012, the optimism about the technology's scientific potential has grown considerably in just a few years. With the numerous applications CRISPR can offer that suggest more effective solutions to our current issues with genome editing, such as the challenge of achieving more precise and accurate modifications of our genome, Doudna's and Zhang's teams are willing to incur the expenses and time to battle for the rights to use CRISPR. There is additional incentive to undergo this CRISPR patent dispute, because the team that is granted those rights will reap the profit that comes from licensing this technology to other companies.

[39] Yeadon, P. J. (2014, March 4). Pros and cons of ZNFs, TALENs, and CRISPR/Cas.

Ethical Implications

In the 1970s, Hebert Boyer founded Genentech, the first biotechnology company. Since then, the biotechnology industry has undergone significant advances. The 1980s brought the first biotech drugs available on the market. In the 1990s, the first genetically-engineered food product, the Flavr Savr tomatoes, were commercialized. Today, genome-editing technology is setting the stage for new biotechnology products, but this new technology also introduces risk and ethical dilemmas.

Society's struggle with addressing the ethical use of genome-editing technologies is not new. In response to Boyer and Cohen's development of recombinant DNA technology in the 1970s, in public hearings hosted in local communities, people articulated their safety and misuse concerns about this new, unfamiliar technology.[40] At that time, scientists were confident that recombinant DNA technology would offer significant opportunities; however, the potential risks of using it in the lab were unclear. In February 1975, scientists organized the Asilomar Conference to set standards for conducting research with recombinant DNA technology without endangering public safety and health. Ethical implications of this technology were not discussed at the conference, however. Scientists had not considered the implications beyond the lab at this time, because they did not see the importance of addressing those downstream implications. This conference marked the start of public discussion on scientific policy

[40] Rosenblatt, D. P. (1982, August 1). The Regulation of Recombinant DNA Research: The Alternative of Local Control.

involving genomic-engineering. Since then, a myriad of new genome-editing issues have surfaced, such as stem cell research and cloning, suggesting that public concerns about the ethical implications of genome-editing technologies have become more complex and pose greater risks in the transition of these technologies from the lab to the market.[41] Addressing the potential ethical implications of utilizing genome-editing technologies is one of the critical steps towards responsible development and application of the technologies.

Throughout the Flavr Savr tomato's short-lived commercial run, consumers' demand for the tomatoes surpassed its supply. During this time, public concern over the "antisensed" tomatoes was not an issue. Calgene's transparency about tomato experiment results and the use of antisense technology in the crop inspired consumers' good will.[42]

Antisense technology in the Flavr Savr tomato case study did not include DNA from another organism – the antisense PG gene came from manipulating the PG gene in a tomato, similar to how a human's own cells were edited with CRISPR to correct for sickle cell. In both cases, DNA from another organism was not introduced. The genetic

[41] Finegold, D. L., Bensimon, C. M., & Daar, A. S. (2005). *Bioindustry Ethics*. Amsterdam: Elsevier.
[42] *Test Tube Tomato* [Video file]. (2013, June 24).

modification was minimal in the tomatoes, another reason why there were fewer ethical concerns about the use of this technology to develop Flavr Savr tomatoes.

Currently, there are two main ethical concerns about human genome-editing. One concern involves making heritable, permanent changes to the germ line, or the sperm and egg cells. A second concern involves the safety of the technology, ensuring that off-target effects are minimal. Using CRISPR to fix sickle-cell anemia involves editing a patient's own cells outside of the body. This process of editing avoids off-target effects, since these edited stem cells will populate in the bone marrow to make other blood cells. Researchers involved with the UC Berkeley Innovative Genomics Initiative are attempting to improve the safety of utilizing CRISPR by conducting experiments with greater numbers of lab animals. With a greater study sample, researchers can more easily identify what lab methods and modifications to the CRISPR system will contribute to the safe use of CRISPR. The focus to improve safety in using CRISPR to correct for sickle-cell anemia involves reducing the likelihood of off-target effects that could lead to other serious diseases, such as beta thalassemia, another type of genetic blood disorder.

In both antisense technology and CRISPR, off-target effects are still a significant concern. It is unrealistic to presume that a tool can be 100% accurate and precise, but we can strive to get close to that level of accuracy and precision. The multitude of potential applications for CRISPR is unique to this technology, especially since it has the

ability to make applications like enhancement and personalized medicine that were once just fantasies become realities, but the off-target effects can serve as a hindrance to these developments. This safety concern explains why scientists are working to continue improving the structure and mechanisms of the CRISPR technology. More complex than the ethical concerns in the Flavr Savr tomatoes, the use of CRISPR in the sickle-cell anemia case study is just one potential application of this versatile technology. So in addition to improving CRISPR's safety, ethical guidelines that address how we will use CRISPR is also necessary to ensure responsible applications of it.

Convergence of Science and Business

The commercialization of the Flavr Savr tomato involved certain areas of contention between the Calgene scientists and its business executives: the lack of communication, the culture clash between management and scientists, and the lack of business expertise. In the late 1980s, Calgene was a science-based company that wanted to enter the fresh tomato business by itself, but the company and the Flavr Savr tomato's eventual demise was due to Calgene's inability to manage the expenses associated with commercializing the tomato. There was not an issue behind the science that created the Flavr Savr tomato.[43]

[43] Martineau, B. (2001). *First Fruit: The Creation of the Flavr Savr Tomato and the Birth of Genetically Engineered Food*. London: McGraw-Hill.

Today, more academic institutions are becoming involved in commercializing the CRISPR technology by creating biotechnology companies invested in exploiting this technology. Equipped with the scientific knowledge of working with CRISPR, academic institutions collaborate with business professionals, who have the knowledge to help move the technology onto the market, to establish biotechnology companies. As a result, scientists and business professionals and their differences in work culture and style will be intersecting more frequently. Reflecting on the lessons from the contention between Calgene's scientists and management that contributed to the company's inefficient commercialization operations, we can observe that if the differences between science and business are not being addressed, both scientists and business professionals, respectively, will be working inefficiently alone while attempting to bring CRISPR to consumers together.

Conclusion

CRISPR's emergence as a new genome-editing technology has resulted in a fivefold increase in investments in the genome-editing market over the past year. Additionally, in 2015, several CRISPR biotechnology companies, including CRISPR Therapeutics and Editas Medicine, received $550 million in investments. This investment was a twofold increase of 2013 and 2014's aggregate investments.[6] From these facts, we can comprehend how plans to commercialize CRISPR appear to be inevitable. CRISPR has been lauded for its ease of use, remarkable precision, and relative low cost to other genome-editing technologies like zinc-finger nucleases (ZFNs). These promising characteristics of CRISPR are disrupting the way researchers conduct research, shortening experiment times, and consequently increasing efficiency. With CRISPR's customizable, relatively precise targeting system to edit genomes, scientists are optimistic that this technology can be utilized in a wide range of applications.

Commercialization of CRISPR largely depends on the collaboration between science and business. Addressing the legal and ethical considerations are important to ensure that commercialization can occur. However, the *process* of commercialization directly involves scientists and business professionals. The simplified commercialization process involves scientists working with CRISPR in the lab and business professionals marketing and selling CRISPR applications on the market. When academic institutions

plan on commercializing CRISPR, scientists often cannot commercialize it on their own; scientists seek to collaborate with people in business who may have more resources and expertise in making the transition from lab to market smoother. Therefore, for academic institutions to commercialize genome-editing technologies like CRISPR, it is important to ensure there is minimal language and culture disconnect between science and business that could make the commercialization process more inefficient.

To work towards bridging any disconnect, we should aim to continue promoting open, ongoing conversations among scientists, ethicists, and the general public about the risks and benefits of CRISPR and about the commercial considerations of this technology. In contrast to the time of the 1975 Asilomar conference when most scientists who conducted recombinant DNA research worked in public institutions, today many scientists are also working in private companies and the issues are wider and more complex in scope, involving the safety of CRISPR, the ethics of its use in germline editing, the legal consequences of the CRISPR patent dispute, inter alia.

At the time of the Asilomar conference, scientists worked in public institutions when government funding for research was not as limited and the competition for grants was not as intense as they are today.[44] As a result, scientists were able to freely express their opinions about recombinant DNA technology without being concerned

[44] Howard, D. J., & Laird, F. N. (2013). The New Normal in Funding University Science. *Issues in Science and Technology,* (1).

that their opinions might affect the amount of research funding they could attain. Now, with more scientists working at private companies, scientists are more focused on the commercial opportunities of genome-editing technologies. With reduced allocation of the federal budget to research and development, locating funding becomes paramount. However, scientists today are increasingly more cautious about disclosing their opinions on these technologies or communicating the technologies' risks, because being transparent about potential risks may make attaining funding more difficult.

Conferences, such as the 2015 International Summit on Human Gene Editing, where scientists and nonscientists worldwide gather to exchange their respective concerns and questions about the applications of genome-editing technologies, should continue to be hosted. There are potential challenges and questions that should be considered with hosting these international discussions across countries and cultures, including the feasibility of organizing a large-scale conference on a more frequent basis or whether we can even formulate a general consensus among the diversity of opinions. Having scholars from other disciplines like the social sciences and business participate and express their viewpoints in these conferences can better reflect the nuanced interests of the general public.[45] Although it may be premature to assign a value to the effectiveness of an international conference just based on our experience from the 2015

[45] Addison, Courtney, and Samuel Taylor-Alexander. "Gene Editing and Germ-line Intervention: The Need for Novel Responses to Novel Technologies." *Molecular Therapy* 23.11 (2015): 1678-680. Web.

summit, having an open setting where conference participants can view all the potential situations involving the use of these technologies and have the opportunity to grapple with those situations can begin to foster more public trust in how scientists and policy makers are approaching this issue of using genome-editing technologies responsibly. With a range of stakeholders involved in the discussion on the use of CRISPR and other genome-editing technologies, stakeholders can reflect on issues from others' perspectives and possibly achieve greater understanding for others' viewpoints.[46]

Within science-based businesses developed from academic institutions, for example the creation of Caribou Biosciences from UC Berkeley, collaboration between scientists and business professionals is inevitable – since these scientists aim to develop their research in CRISPR and other genome-editing technologies to benefit others, scientists are partly responsible to inform and engage the general public about their research.[47] For scientists to achieve their goal of transitioning CRISPR from the lab to the market, they must also do their best to understand how business professionals, who provide their business acumen and knowledge of marketing and selling the technology, work.

Business professionals value implementing strong organizational culture in their work places to encourage strong working relationships and efficiency, promoting

[46] Jensen, K. K., Forsberg, E., Gamborg, C., Millar, K., & Sandøe, P. (2010, June 30). Facilitating Ethical Reflection Among Scientists Using the Ethical Matrix.
[47] "Public Dialogue on Genome Editing: Why? When? Who?" (2016): n. pag. Web.

specific company values and management practices. These business practices might be more unfamiliar to scientists, who are seen as more focused on making discoveries from their research. Business professionals should also strive to consider scientists' opinions about commercializing CRISPR and maintain clear communication with and provide regular updates to scientists throughout the entire commercialization process. Although business professionals are tasked with moving the commercialization process of the technology forward, scientists are the ones who are most knowledgeable about how the technology works, its technical risks and benefits, and how its mechanisms can be applied into practical products for the public.

The general public are the end users of applications developed using genome-editing technologies. So, as a measure of encouraging transparent conversation about genome editing and the use of genome-editing technologies, it is critical to listen to the voices of the public. Studies have shown that many of the terms, such as "gene" and "genetics", discussed in debates on genome editing are unfamiliar to the public.[48] Developing community programs or forums can aid in providing the public with resources to learn more about basic jargon used in discussing genome editing. In informal, familiar settings, these forums can give individuals the opportunity to listen and relate to the concerns of other community members. Program moderators could be

[48] Blendon, Robert J., Mary T. Gorski, and John M. Benson. "The Public and the Gene-Editing Revolution." *New England Journal of Medicine* 374.15 (2016): 1406-411. Web.

researchers in the community or representatives from science advisory groups like the National Academy of Sciences that have the resources and knowledge to inform community members about the uses of CRISPR and to respond to the public's questions. Moderators may have roles in science policy making, so they should identify and record community members' main concerns that will be taken into consideration when making policies to determine how we should proceed in using CRISPR.

Opening up conversation to include all stakeholders, not just to scientists and business professionals, can expand our intellectual resources to be available to everyone. As we continue to learn more about CRISPR's mechanisms, make progress in sharpening CRISPR's cuts, and observe the evolving field of gene editing, encouraging ongoing discussion can equip us with up-to-date intellectual resources needed to help address future concerns about commercializing genome-editing technologies.

Ethics training for both scientists and business professionals should also be provided. Scientists participate in ethics training when they are in school and business professionals often undergo ethics training at their workplaces, but in the specific case of commercializing genome-editing technologies like CRISPR, which can have significant implications if not used responsibly, it is crucial to organize specialized trainings. Genome-editing advisory groups and ethics councils, comprised of experts with backgrounds in ethics and research, from academic institutions should organize these CRISPR ethics trainings. Scientists who attend these trainings have the opportunity to

reflect upon and discuss the potential ethical implications of their research with other scientists. These trainings should also aim to teach scientists methods on how they can clearly communicate accurate information about and the ethical implications of CRISPR to nonscientists.

Business professionals would also benefit from attending ethics trainings that inform participants on what the general risks of CRISPR are, not delving into the technical challenges, so that these professionals can comprehend the importance of making ethical decisions throughout the commercialization process. Also, the ethics trainings should discuss ways by which business professionals can help scientists communicate the ethical uses of CRISPR. Business professionals are coming from the perspective of a nonscientific group, so these professionals can provide insights to scientists about how to more effectively communicate with nonscientists.

Due to different individuals' opinions about what ethics topics are considered most critical for scientists and business professionals to learn, there may be disagreement among ethics councils and genome-editing advisory groups on deciding what content the ethics trainings should cover. The ethics councils and advisory groups should seek to find common ground on the most salient ethics topics that the majority of the individuals believe must be addressed in the trainings. Just as ethical guidelines that provide general directions on how we should proceed with the use of CRISPR are

difficult to develop, determining the content of ethics trainings for scientists and business professionals is challenging to implement, too.

The advances in genome editing and genome-editing technology are innovative and changing how scientists conduct research, how business professionals are choosing to invest in life-science companies, and how the general public approaches disease, human health, and the ways in which we live our lives. With the introduction of CRISPR, the field of genome-editing technology is living through a time when we have a "higher threshold for trying something risky because the benefit could be so remarkable."[49]

[49] New Gene-Editing Techniques Hold the Promise of Altering the Fundamentals Of Life. (2017, January 12).

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Biography

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